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7. (Amended) A method of claim 1 wherein said [therapeutic] gene product is foreign to said cells.

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8. (Amended) A method of claim 1 wherein said gene product [of said therapeutic gene] is toxic to said cells.

9. (Amended) A method of claim 8 wherein said gene product [of the therapeutic gene] induces apoptosis.

Please add the following new claim:

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--46. The method of claim 1, wherein said cells are present within a mammal.--

REMARKS

Claims 1-45 are pending, with claims 1-12 currently under consideration. In the Office Action dated April 10, 2000, claims 1-12 were rejected under 35 U.S.C. § 112, first and second paragraphs, and under 35 U.S.C. § 103. Each of these rejections is addressed in turn below. Support for the present amendment to claim 1 can be found, *e.g.*, at page 4, lines 18-20. Support for new claim 46 can be found, *inter alia*, at page 5, lines 8-29. No new matter has been added.

Restriction requirement

In the Office Action, the Examiner states that the election of Group I made in the Response of March 9, 2000, is considered as having been made without traverse because the Response allegedly did not distinctly and specifically point out the supposed errors in the Restriction requirement.

In response to this statement, Applicants submit that the Response did indeed distinctly and specifically point out the supposed errors in the restriction requirement, and should thus be considered as having been made with traverse. Specifically, the Response stated:

> The foregoing election is made with traverse as the three group set out by the Examiner all stem from a common concept and theory and are thus related. As such, prosecution of the claims of

> Groups I-III would not place a substantially greater burden on the Examiner. *See*, page 1 of the Response dated March 9, 2000.

Indeed, each of the three groups involves essentially similar methods, as each group comprises exposing cells to electromagnetic radiation to synchronize the cells, and subsequently transfecting the synchronized cells with a nucleic acid. The only differences between the three groups involve the type of cells that are synchronized and/or the particular identity of the nucleic acids used. As such, as stated in the Response of March 9, 2000, each of the groups indeed stem from a common concept and theory, involving the same essential steps, and would thus not place a substantially greater burden on the Examiner. Accordingly, the reasons set forth in the Response for traversal are sound. *See, e.g.*, MPEP § 803.

It is noted, incidentally, that the Examiner appears to mischaracterize the methods of Group I in the Restriction requirement, as the term "transformation" in these claims is apparently taken by the Examiner to refer to the acquisition of cancerous properties in a cell, rather than the intended meaning of introducing a nucleic acid into the cell. Accordingly, the Examiner's statement that the methods of group I to "transform cells to grow" is "exactly opposite" to the claims of group II is incorrect. While Applicants believe that the use of the term "transformation" in original claim 1 was clear, it is noted that claim 1 has been amended to refer to "transfection" of a cell.

In view of the above, Applicants respectfully submit that claims 1-45 should be examined together, or, at the very least, that the Response dated March 9, 2000, should be considered as an election with traversal.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1-12 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly lacking enablement. Specifically, the Examiner asserts that while the specification is enabling for cells sensitive to electromagnetic radiation, and for the use of X-rays, the specification is allegedly not enabling for the synchronization of radiation insensitive cells or for the use of radiation other than X-rays. Applicants respectfully traverse this rejection.

The Examiner first asserts that many cell types are insensitive to the effects of radiation and other cell synchronizing agents, and that the claims are therefore enabled only for

the transformation of cells that are sensitive to electromagnetic radiation. In support of this assertion, the Examiner alleges that Vogelstein *et al.* ("Vogelstein") describe p21 deficient cells that are defective in cell cycle check point control and thus cannot be synchronized by agents such as radiation. The Examiner asserts that these cells "would not be altered by radiation and therefore, the efficiency of transformation would not be affected by the method recited in the claims." *See*, page 3 of the Office Action. Applicants reply, first, that the possibility that some cells may be insensitive to radiation does not in and of itself indicate that the claims are not enabled, and, second, that this is a mischaracterization of the teachings of Vogelstein.

The test of enablement is whether, at the time of filing, one of skill in the art would have been able to make and use the claimed invention without undue experimentation. *See, e.g.*, MPEP § 2164. Further, for a proper rejection of the claims for lack of enablement, the burden is on the Examiner to provide a reasonable basis to question the enablement of the claims. *See, e.g.*, MPEP § 2164.04. Thus, in the present case, the Examiner's assertion that some cells may be resistant to electromagnetic radiation is not by itself a sufficient basis for a rejection under § 112, first paragraph, for lack of enablement. Instead, a proper enablement rejection would require a demonstration that the potential resistance of some cells to electromagnetic radiation would impose a requirement on one of skill in the art to engage in undue experimentation in order to make and use the present invention. As the Examiner has not made such a demonstration, this rejection should be withdrawn.

Further, Applicants submit that even if some cells were in fact resistant to electromagnetic radiation, this would not impose an undue burden on one of skill in the art to practice the invention. Instead, this would simply require, at most, an assessment of the radiation sensitivity of cells prior to the practice of the claimed methods. Assays for determining the effects of an agent such as radiation on the cell cycle were routine in the art at the time of filing, and are described, *e.g.*, in the specification as filed (*see, e.g.*, page 47, line 3 to page 48, line 4), as well as in certain references cited by the Examiner (*see, e.g.*, Vogelstein *et al.* and Spang-Thomsen *et al.*). Accordingly, the possibility that some cells may be resistant

to electromagnetic radiation or other cell cycle blocking agents would have in no way imposed a requirement for undue experimentation on one of skill in the art.

Further, and in contrast to the Examiner's assertions, Vogelstein in fact clearly and explicitly teaches that even in checkpoint deficient cells, ***DNA damage causes a cell cycle arrest***. For example, column 2, lines 41-44 of Vogelstein state:

> In the absence of a functional cell cycle checkpoint, ***DNA damaged cells arrest in G2*** but then undergo additional S phases without intervening normal mitoses. (Emphasis added).

Further, Vogelstein explicitly states that in their experiments, while the profile of cell cycle arrest was altered, p21 mutant cells were efficiently synchronized by cell cycle blocking agents at the G2 phase of the cell cycle:

> Following 30 hours of exposure of Adriamycin, p21+/+ cells were blocked in G1 and G2 phases, with few cells in S (Fig. 3c). In contrast, no G1 block was evident in the p21-/- cells, so that ***a nearly pure population of G2-arrested cells was observed*** (FIG. 3d).

Thus, Vogelstein clearly teaches that p21 deficient cells can in fact be synchronized by common agents such as electromagnetic radiation. Accordingly, even if it were relevant to the enablement of the claims, the Examiner has not in fact demonstrated that some cells are resistant to electromagnetic radiation.

The Examiner also asserts that the claims are not enabled for the use of electromagnetic radiation other than X-rays. Specifically, the Examiner asserts that, while the evidence provided in the specification demonstrates that chemical agents can be used to synchronize cells and increase the efficiency of transformation, and that X-rays can be used to increase the efficiency of transformation, the specification allegedly provides "no example nor guidance" to support the effect or ability of other forms of radiation to affect the cell cycle of a cell. Further, the Examiner asserts that because the mechanism for cell cycle synchronization by X-rays is not described in the specification or the art of record, one cannot "assume an inherent ability of all electromagnetic radiation to regulate the cell cycle in a similar manner." *See*, pages 3-4 of the Office Action.

As discussed *supra*, the Examiner has the burden of establishing that a particular claim lacks enablement, and that it is not up to the Applicants to provide working examples for each embodiment of the claimed invention, as the Examiner appears to be requiring by this rejection. Applicants remind the Examiner that the basis of the present invention, as clearly spelled out in the specification, is that any agent that causes cell cycle synchronization, such as electromagnetic radiation, can be used to practice the invention. The specific identity of the agent is not essential, nor is the precise mechanism of the cell cycle block caused by the agent, *e.g.*, DNA damage in the case of X-rays. Whether a mechanism is explicitly described or not is irrelevant to the enablement of the claims, as is whether one can "assume an inherent ability of all electromagnetic radiation to regulate the cell cycle in a similar manner." The question is simply whether, at the time of filing, one of skill in the art would have been able to identify, without undue experimentation, forms of electromagnetic radiation that could have been used to synchronize cells. As the Examiner has not demonstrated that such undue experimentation would have been required, this basis for rejection is unfounded and the rejection should be withdrawn.

Further, this basis for rejection is surprising in view of the assertions made by the Examiner in support of the rejection of the present claims under § 103, where it is asserted that one of skill in the art would have had a reasonable expectation of success to practice the invention using any form of cell cycle blocking agent:

> There would have been a reasonable expectation of success given the results that different methods of synchronization were effective in increasing the transformation efficiency and thus cell cycle dependent suggesting that ***any form of synchronization would be effective*** including the x-ray radiation taught by Spang-Thomsen et al. *See*, page 6 of the Office Action. (Emphasis added).

As art serving as a basis for a rejection under 35 U.S.C. § 103 must itself be enabling (*see, e.g.*, MPEP § 2121), it is clearly improper for the Examiner to impose one enablement standard for the present claims, and another, much lower standard, for the prior art.

Nevertheless, regardless of whether or not the Examiner has established a proper basis for an enablement rejection of the present claims, Applicants submit that one of

skill in the art would have been readily able to identify suitable forms of electromagnetic radiation without undue experimentation.

First, at the time of filing, a number of forms of radiation were known in the art to be capable of blocking the cell cycle, including, for example, X-rays, UV rays, and gamma rays. (*See, e.g.,* Bolognia *et al.* (1994); Rubin *et al.* (1988); both enclosed). Further, as discussed *supra,* one of skill in the art would have been able to assess the ability of any particular form of electromagnetic radiation to synchronize cells using any of a number of routine assays for determining the effect of an agent on the cell cycle. Accordingly, in view of the variety of forms of electromagnetic radiation already known to block the cell cycle, and in view of the ease with which one of skill would have been able to assess the ability of any form of electromagnetic radiation to synchronize cells, Applicants submit that the present claims are fully enabled for the use of any form of electromagnetic radiation.

Finally, the Examiner alleges that claims 3-5 are not enabled because the specification allegedly lacks guidance or examples to demonstrate that cells can be synchronized with X-rays in any other state than G2/M. Applicants do not fully understand this rejection, as the Example describing the use of X-rays does not specify that the cells were synchronized at G2/M. In any case, as discussed *supra* regarding the other bases of rejection, Applicants emphasize that they are not required to provide evidence that X-rays or other forms of electromagnetic radiation could have been used to synchronize cells in the various stages of the cell cycle. Instead, a proper rejection of these claims under 35 U.S.C. § 112, first paragraph, must be based upon objective reasons why the claims are not enabled. In the absence of any such reasons, this rejection is improper and should be withdrawn.

Nevertheless, the present claims are fully enabled for the use of electromagnetic radiation to synchronize cells in different parts of the cell cycle. Indeed, it was known in the art at the time of filing that electromagnetic radiation such as X-rays can cause cell cycle delay or arrest in different parts of the cell cycle, including G1 and G2 phases. *See, e.g.,* Pellegata *et al.* (1996), enclosed. Therefore, one of skill in the art would have been clearly capable of synchronizing cells in any phase of the cell cycle in order to practice the claimed invention. Accordingly, these claims are fully enabled by the specification as filed.

In view of all of the above, Applicants respectfully submit that the present claims are fully enabled by the specification as filed. Accordingly, Applicants request that the rejections of the pending claims under 35 U.S.C. § 112, first paragraph, be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

Claim 1 was rejected under 35 U.S.C. § 112, second paragraph, because it is allegedly unclear whether the term "transformation" refers to the introduction of a nucleic acid into a cell or the acquisition of cancerous properties in a cell. Applicants have amended claim 1 to refer to the "transfection" of a cell, thereby obviating this rejection.

Claims 7, 8 and 9 were rejected because the phrase "said therapeutic gene" lacks antecedent basis. Each of these claims has been amended to remove this discrepancy.

Rejections under 35 U.S.C. § 103

Claims 1-9, 11 and 12 were rejected under 35 U.S.C. § 103 as allegedly obvious over Yorifuji *et al.* ("Yorifuji") in view of Spang-Thomsen *et al.* ("Spang-Thomsen"). Specifically, the Examiner alleges that Yorifuji teaches that G2/M is the most efficient period for transformation, and that Spang-Thomsen teach that cells can be synchronized using X-rays. Applicants respectfully traverse this rejection.

A *prima facie* case of obviousness requires the presence of each claim element in the prior art, a motivation or suggestion to combine or modify these elements to achieve the invention, and a reasonable expectation of success. *See, e.g.*, MPEP § 2143.02. As discussed *infra*, the Examiner has failed to establish that such a reasonable expectation of success exists in the present application.

It is emphasized that the presently claimed methods read upon *in vivo* methods of synchronizing and subsequently transfecting cells. The present application provides numerous working examples, using various compounds as well as with electromagnetic radiation, demonstrating that cells can be synchronized *in vivo* and transfected with nucleic acids, resulting in a dramatic increase in the level of expression of the nucleic acids. The *in vivo* aspect of the claims of Group I are set forth more explicitly in new claim 46, which specifies that the cells are present "within a mammal."

The first reference cited by the Examiner, Yorifuji, provides no guidance whatsoever regarding the introduction of nucleic acids into cells *in vivo*. Specifically, this reference simply describes the *in vitro* transfection of cells at various periods of the cell cycle, and provides no suggestion, let alone a demonstration, that such methods could be practiced *in vivo*. Accordingly, in view of the unpredictability of *in vivo* methods of gene delivery, this reference would not have provided a reasonable expectation of success for one of skill in the art to practice the claimed methods.

Further, a number of statements in Yorifuji suggest that their findings may be limited to the particular method of transformation used in their experiments, *i.e.*, electroporation. For example, the title of the article is, "The effect of cell synchronization on the efficiency of stable gene transfer ***by electroporation***." (Emphasis added). In addition, the concluding sentence of the abstract, which is also found in the discussion section of the article, states, "These results suggest that the G_2/M phase is the most efficient period for stable gene transfer ***by electroporation***." (Emphasis added). Therefore, this reference would not have provided a reasonable expectation of success for *in vitro* methods of transfection other than by electroporation, let alone for *in vivo* methods.

The second reference cited by the Examiner, Spang-Thomsen, also fails to provide a reasonable expectation of success. Specifically, while Spang-Thomsen report some synchronization of cells *in vivo*, they emphasize in numerous places the fact that very few cells were synchronized in their experiments. For example, the abstract of the reference states:

> The results showed that the treatment initially induced ***a partial synchronization of small fractions of cells*** accumulated in the G phase of the cell cycle and a dose-dependent decrease of the cell generation time due to a shortening of the G2 duration time during regrowth of the tumours. (Emphasis added).

Because of these poor results, Spang-Thomsen actually explicitly raise doubts about the usefulness of their findings for therapeutic applications:

> It is questionable whether cell accumulation of this magnitude could be utilized in the design of fractionated radiotherapy to increase the treatment effect. *See*, page 852, column 2.

Thus, if anything, Spang-Thomsen would had led one of skill in the art to believe that *in vivo* methods of cell cycle synchronization using X-rays were not generally effective.

In view of the above, Applicants submit that one of skill in the art would not have accepted that one reference that describes results obtained with one particular type of transfection *in vitro*, and another that emphasizes the small number of cells synchronized using X-rays, would have provided a reasonable expectation of success to practice the claimed invention. Therefore, as a reasonable expectation of success is essential for the establishment of a *prima facie* case of obviousness, the present rejection under 35 U.S.C. § 103 is improper and should thus be withdrawn.

Claim 10 was rejected under 35 U.S.C. § 103 as allegedly obvious over Yorifuji in view of Spang-Thomsen, as applied to claims 1-9 and 11, and further in view of Son *et al.* ("Son"). According to the Examiner, independent claim 1 is obvious in view of Yorifuji and Spang-Thomsen, as discussed *supra*, but does not teach transformation using a lipid-nucleic acid particle, which is allegedly taught by Son. Applicants respectfully traverse this rejection. It is noted, incidentally, that while the first paragraph of page 7 refers to "Lechardeur *et al.*" instead of Son *et al.*, Applicants assume that the correct reference is Son. Clarification is requested if this assumption is incorrect.

As noted above, one of skill in the art would not have had a reasonable expectation of success to make and use the claimed invention based on the teachings of Yorifuji and Spang-Thomsen. Accordingly, as such an expectation of success is required for a *prima facie* case of obviousness under 35 U.S.C. § 103, claim 1 is indeed patentable over these references. Therefore, as a claim that is dependent from a nonobvious claim is itself nonobvious (*see*, MPEP § 2143.03), Applicants submit that dependent claim 10 is indeed patentable under 35 U.S.C. § 103.

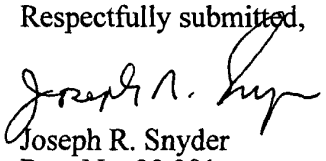
In view of all of the above, Applicants respectfully submit that each of the pending claims are nonobvious over the cited prior art. Accordingly, Applicants request the withdrawal of the pending rejections of the claims under 35 U.S.C. § 103.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at 415-576-0200.

Respectfully submitted,



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Attachments: Bolognia *et al.* (1994)
Rubin *et al.* (1988)
Pellegata *et al.* (1996)

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